## REMARKS/ARGUMENTS

Claims 48-59 are pending in the present application.

Applicants note that they never received an Examiner-initialed copy of the 1449 forms filed on January 2, 2004 and on January 30, 2001 (courtesy copies attached) and accordingly, respectfully request that the Examiner initial the aforementioned 1449 forms and attach it to the next communication mailed to Applicants.

## REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH

The Examiner rejected claims 48-55 and 57-59 under 112, first paragraph because the specification does not enable one skilled in the art to "make and/or use the invention commensurate in scope with these claims" (page 3 of Office Action).

In response to Applicants' arguments in the Amendment filed January 2, 2004, the Examiner states that "the attachment of an 8-40 carbon lipophilic group optionally via a spacer to the C-terminal amino acid of GLP-1 is enabled" and that "methods for preparing analogs of GLP-1 were well known to one of ordinary skill in the art" (page 7 of Office Action) but nonetheless rejects the claims as nonenabled because "the identities of the active GLP-1 analogs are not provided, thus it is necessary to have additional guidance and to carry out further experimentation to assess the effects of derivatives containing the various GLP-1 analogs" (page 7 of Office Action).

In particular, the Examiner alleges that the claims encompass many variants of GLP-1 analogs for the derivatives and that "the specification does not provide sufficient teachings regarding the identities of these variants and their pharmacological effects", stating as an example that "the protraction of SEQ ID NO:2 or any derivative containing GLP-1 is not demonstrated" (page 7 of Office Action).

Applicants respectfully traverse this rejection.

The test of enablement is whether one reasonably skilled in the art could make

and use the invention from the disclosure in the application coupled with information known in the art without undue experimentation. In this regard, it is well settled that a patent application need not teach what is known in the art and that the fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. Further, the presence of inoperative embodiments within the scope of a claim does not render a claim invalid if one skilled in the art could determine which embodiments were operative or inoperative with expenditure of no more effort than is normally required in the art.

Here, the pending claims are directed to C-terminally modified GLP-1 or analogs thereof where the modification is the attachment of an 8-40 carbon lipophilic group optionally via a spacer, to the C-terminal amino acid of the aforementioned GLP-1 or analogs thereof.

The application teaches that analogs of the parent peptide are peptides that have qualitatively the same pharmacological effect as the parent peptide, that the derivatives of the invention have a protracted profile of action relative to the unmodified parent peptide (ie to unmodified GLP-1 or an unmodified analog thereof), and that one measurement of protraction can be obtained by measuring the disappearance rate of the derivatives in pigs following subcutaneous injection (see page 2, lines 14-18 and page 12, line 36 to page 13, line 26 of the application).

Regarding information known to the skilled artisan as of the present application's earliest priority filing date of March 17, 1995, it was known that:

1) a pharmacological effect of GLP-1 was its ability to stimulate insulin release in vitro or in vivo and the ability to stimulate cAMP production (see pages 7-12 of WO 91/11457, copy attached);

2) the receptor for GLP-1 had been cloned (see WO 93/019175, copy attached) and screening assays using the receptor had been described to identify GLP-

1 analogs that were GLP-1 agonists (see Example 3 and claim 15 of WO 93/019175);

3) structure-activity studies of GLP-1 had identified specific residues of GLP-1 that could be changed without significantly affecting its biological activity [see, for example, Table 1 of Adelhorst et al (1994) J. Biol. Chem., 269: 6275-6278, Watanabe et al (1994) J. Endocrinol., 140:45-52 and Gallwitz et al (1994) Eur. J. Biochem., 1151-1156, copies attached]; and

4) additional specific GLP-1 analogs had been described (see, for example, WO 91/11457).

Thus, as of the priority filing date of the present application, it was known which residues in GLP-1 could be varied to produce GLP-1 analogs having a qualitatively similar effect as the parent GLP-1 peptide and specific analogs had been described as had methods for identifying further analogs.

Moreover, the Knudsen et al [J Med Chem (2000) 43: 1664-1669] reference cited by Applicants in the previous Amendment as providing 3 examples of analogs acylated at the C-terminus [ie compounds 8, 27 and 35 of Table 1] which exhibited a protracted plasma half-life relative to GLP-1 (7-37) following subcutaneous administration to pigs (ie the methodology disclosed on page 12, line 36 to page 13, line 26 of the present application); further discloses that :

1) an analog of GLP-1 (7-36) modified at amino acid 36 with different length fatty acids had activity (see compounds 26-28 in Table 1 and the first paragraph on page 1667);
2) four different GLP-1 (7-38) analogs modified at amino acid 38 with different length fatty acids were "very potent" (see compounds 9 and 29-35 in Table 1 and the second paragraph on page 1667); and
3) "the peptide hormone GLP-1 could be derivatized almost anywhere in the C-terminal part of the peptide" (page 1667, Conclusion section).

Accordingly, Applicants submit that given the teachings of the specification and the information known in the art as of the priority filing date of the present application, the question of whether one reasonably skilled in the art, based on the disclosure in the application coupled with information known in the art could make and use the presently claimed invention without undue experimentation, must be answered in the affirmative. It is Applicants' position that to do otherwise and limit applicants to the single GLP-1 derivative exemplified in the application (ie claim 56) would unfairly allow potential infringers to use the teachings of the application to design around such a claim.

Accordingly, in view of the above arguments and references presented herein, Applicants submit that pending claims 48-59 are fully enabled by the present application and withdrawal of this rejection is respectfully requested.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Please charge any deficiencies or overpayment to Deposit Account No.14-1447.

Respectfully submitted,

Date: December 15, 2004

Richard W. Bork, Reg. No. 36,459
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

**Use the following customer number for all correspondence regarding this application**

23650
PATENT TRADEMARK OFFICE